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## A CONTRIBUTION TO THE CASUISTRY OF PLACENTAL AND CONGENITAL TUBERCULOSIS.\*

MILINARY TUBERCULOSIS OF THE MOTHER IN SEVENTH MONTH OF PREGNANCY; TUBERCULOSIS OF PLACENTA; AGGLUTINATION THROMBI, CONTAINING MANY TUBERCLE BACILLI, IN PLACENTA AND FETUS.

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THE ancient problem, which so long busied clinicians and pathologists, as to the occurrence of a direct transmission of tuberculosis from the parent to the child, has, in so far as a maternal transmission is concerned, been settled beyond all doubt by a number of trustworthy observations based upon both anatomical and bacteriological findings. The frequency of such a transmission, however, must still be regarded as an open question. The dictum accepted by most writers at the present time, that the intra-uterine transmission of tuberculosis is possible, but extremely rare, needs the support of further research before it can be taken as final. It is true that but few undoubted cases of tuberculosis of placenta and fetus have been reported; but it is also true that no field of research has been so neglected as that of placental and fetal pathology. To what extent are systematic examinations of placentas made? In view of this neglect, it is not surprising that but few positive cases of placental and fetal tuberculosis have been observed; and some reason is afforded for the belief that those conditions are probably not so rare as they are at the present time supposed to be.

Further support is given to this belief by the fact that there is a constantly increasing number of cases reported in which an intra-uterine transmission of infectious diseases has been demonstrated beyond all doubt. Such a transmission from the mother to the fetus has been shown to occur in the case of small-pox, varicella, typhus fever, typhoid fever, relapsing fever, malaria, scarlatina,

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measles, anthrax, cholera, and infections with the pneumococcus and pus-cocci. While the number of such cases is on the whole not great, it is nevertheless increasing in proportion to the increasing frequency with which systematic examinations of the placenta and fetus are being carried out.

The greater frequency with which careful examinations have been made of the placenta and fetus of cattle and the large number of cases of bovine placental and congenital tuberculosis which have been reported strongly support the view that these conditions may not be so rare in man, and might be discovered more frequently were similar systematic observations made. The results of veterinary investigation, even though the latter be somewhat loosely carried out, favor the occurrence of placental transmission as a more frequent event than is generally believed.

As a result of these observations we have been obliged to modify somewhat our views concerning the rôle played by the placenta as a filter of micro-organisms contained in the maternal blood. At the present time the view is held by a preponderating majority of writers that the intact syncytial layer of the chorion forms a secure barrier against the passage of micro-organisms from the maternal to the fetal blood. There are several reasons, both clinical and pathological, for doubting the effectiveness and completeness of such protection. Before final dicta are accepted it will be necessary to enlarge greatly the casuistry of placental transmission; and it is desirable that large series of observations upon the fetus and placenta should be studied. The case described below is reported toward this end, as well as for its more immediate bearings upon the pathology of tuberculosis.

A number of writers have collected and analyzed the cases reported in the literature as congenital tuberculosis. Among the most important of such analyses are those of Gärtner,<sup>1</sup> Hauser,<sup>2</sup> D'Arrigo,<sup>3</sup> and Cornet.<sup>4</sup> A more or less complete bibliography is given by each one of these authors. It will be seen, however, from a survey of the cases analyzed by these writers that many

<sup>1</sup> *Zeit. für Hyg. u. Infektionskrankh.*, 1893, 13, 101-250.

<sup>2</sup> *Deutsches Arch. für klin. Med.*, 1898, 61, 221.

<sup>3</sup> *Centralbl. f. Bakteriöl.*, 1900, 28, 683.

<sup>4</sup> *Nothnagel Spec. Path. u. Ther.*, 1900, 14, 2, Abt. 2,

cases which have been regarded as undoubted examples of congenital tuberculosis have been diagnosed as such upon insufficient grounds, the evidence, both bacteriological and anatomical, being inadequate for the support of such a diagnosis. In but few cases is it possible to say positively that a placental transmission of tuberculosis had taken place, the other cases being doubtful because of the lack of bacteriological or anatomical evidence, the age of the child, possibility of extra-uterine infection, non-elimination of syphilis, etc. For this reason it will be of value to analyze again all such reported cases more closely than has previously been done, and to bring the bibliography up to the present date. In the analysis given below we have taken as criteria for the diagnosis of undoubted congenital tuberculosis the presence of characteristic anatomical changes and of tubercle bacilli, the development of the lesions within such a short time after birth as to preclude the possibility of extra-uterine infection, and the exclusion of syphilis. An analysis based upon such strict conditions has not yet been made, and our results, as given below, will be found to differ greatly from those of preceding writers. Many cases which have been regarded as undoubted examples of congenital tuberculosis we have put into the doubtful class, since they did not answer the above requirements so fully as to leave no room for doubt. Further, other cases reported as congenital tuberculosis we have thrown out altogether, since no sufficient proof was given of the nature of the process. The number of undoubted cases, therefore, becomes very small indeed; but a certain number of the cases placed in the doubtful list seem very probable instances of congenital infection, but are not reported with sufficient data to make the diagnosis undoubted.

## I. CONGENITAL TUBERCULOSIS.

### A. UNDOUBTED CASES.

(Diagnosis resting upon anatomical changes and the presence of tubercle bacilli.)

1891, SABOURAUD (*Soc. de Biologie*, Paris, Oct. 17, 1891).

Child aged eleven days, born of mother in advanced stage of pulmonary tuberculosis, who died shortly after delivery. Autopsy of infant showed presence of countless miliary tubercles in liver and spleen, in part showing caseation, and containing tubercle bacilli.

Woman forty years of age, suffering from advanced pulmonary tuberculosis, gave premature birth to a male child in the ninth month. The mother died two days after delivery. Autopsy showed chronic pulmonary tuberculosis, acute miliary tuberculosis of lungs, tuberculous meningitis. Placenta not examined. Child died twenty-four hours after birth. Autopsy showed miliary tuberculosis of lungs, liver, spleen, and kidneys. Tubercles also present in portal, mediastinal, bronchial, mesenteric, and retroperitoneal glands. The microscopical appearance was that of typical tubercles. Large numbers of tubercle bacilli found. No giant-cells present in the tubercles. Advanced stage of the process makes case undoubtedly congenital.

Child fifteen days old. Autopsy revealed typical caseous miliary nodules in spleen, liver, and lungs, containing numerous tubercle bacilli. These were also found free in the blood-vessels. Chronic tuberculous lesions were found in the liver. Mother was brought to hospital with pulmonary tuberculosis after birth of child. Case regarded as undoubtedly congenital, as such advanced lesions could not have formed during the short period of extra-uterine life.

New-born female child weighing 3,060 grams. Died of inanition after a few days. Nothing known of mother. Autopsy of infant showed general tuberculosis, most marked in liver. The spleen was somewhat enlarged, and contained so many tubercles that its surface presented a marbled appearance. Lungs contained a smaller number of tubercles. Brain and retina of both eyes free from tubercles. Large numbers of tubercle bacilli were found in the tubercles and also free in the capillaries. In some sections the bacilli were so numerous that when stained for tubercle bacilli the red areas were visible to the naked eye.

Mother in advanced stage of tuberculosis died three days after premature delivery in the seventh month. Placenta showed numerous caseous tubercles with tubercle bacilli. Inoculation of guinea pigs with portions of placenta gave positive results. Child died on twenty-eighth day. Autopsy showed miliary tubercles in lungs, liver, spleen, and endocardium of right heart. Typical tubercle bacilli present. Inoculation of rabbit with portions of fetal organs gave positive results. The tuberculous endocarditis is of especial interest as the first case noted in infants.

**1894, LEHMANN** (*Berl. klin. Wchnschr.*, 1894, 30, 646).

**1894, HONL** (*Bull. internat. de l'acad. de science de l'emper., F. J. I.*, Prague, 1894).

**1896, USTINOW** (*Arch. f. Kinderheilk.*, 1898, 25, 66).

**1898, AUCHÉ ET CHAM-BRELENTE** (*Munch. med. Wchnschr.*, 1898, 45, 616).

## B. PROBABLE OR DOUBTFUL CASES.

(Diagnosis resting upon anatomical appearances [gross or microscopical] only, without demonstration of presence of tubercle bacilli; or doubtful because of age of child, non-elimination of possible syphilis, extra-uterine infection, etc.)

- 1825, DUPUY** (*Discus. de l'Acad. de Méd.*, 26 Apr., 1825). Dupuy found tuberculosis of the suprarenal in the sixth-month fetus of a phthisical mother. Anatomical evidence only. Doubtful case.
- 1825, HUSSON** (*ibid.*). Found caseating and softened tubercles in the lung of a seven-month fetus of a woman suffering from advanced pulmonary tuberculosis. Evidence anatomical only. Case very doubtful.
- 1852, WEBER** (*Beiträge z. path. Anat. des Neugeborenen*, 1852, 11, 64). Makes the statement that he had many times observed tuberculous cavities of the size of half a lobe in children under the age of three months. Very doubtful.
- 1861, JACOBI** (*Compt. rend. du deuxième congrès de la tuberc.*, 1891, 327). (Not published until 1891.) Seven-month fetus of a mother suffering from chronic pulmonary tuberculosis had numerous caseating tubercles in liver, spleen, pleura, and peritoneum. Probable case. Anatomical evidence only.
- 1868, DEMME** (*Bericht über die Thätigkeit des Jennerschen Kindersp. in Bern*, 1868, No. 6). Two cases. (1) Boy of five weeks. Sick from birth with fever and cough, showed on autopsy caseous nodules in both lungs and infiltration of bronchial and tracheal glands. Mother died of chronic pulmonary tuberculosis soon after delivery. (2) Child died on seventeenth day after delivery. Similar to first case. Tuberculosis in mother shown by physical signs. Both cases doubtful.
- 1873, CHARRIN** (*Soc. des Sci. Méd. de Lyon*, 1873, No. 19). Seven-and-a-half month child of tuberculous mother, died three days after birth. Autopsy showed widespread tuberculosis of abdomen and abdominal organs. Scattered tubercles in lungs. Probable case. Anatomical evidence only.
- 1875, DEMME** (*Bericht über die Thätigkeit des Jennerschen Kindersp. in Bern*, 1875, No. 13). Female child, twelve days old, of tuberculous mother. Autopsy showed caseous bronchial glands, and numerous caseating nodules in both lungs. In right apex and right lower lobe many cavities size of pea to a cherry. Mesenteric glands unchanged. Doubtful case. Anatomical evidence only.
- 1875, MERKEL** (*Ohlendorff Zeitschr. f. klin. Med.*, 1884, 8, Heft 6). (Not reported until 1884 by Ohlendorff.) In January, 1875, patient developed pleuritis, followed by bronchial catarrh and infiltration of apices. In February she conceived. In June showed tuberculous laryngitis. By October patient had to be fed with tube. Child was born on November 4. On the 6th the mother died, autopsy showing tuberculous cavities and miliary tuberculosis. Child was very atrophic; was born with small yellow tumor on hard palate. On second day this discharged cheesy material; abscess then developed in left

greater trochanter. Child died of inanition. Autopsy showed caseous nodule in hard palate infiltrating the bone, caseation of cervical glands, caseous nodule behind left hip joint, not affecting joint. Probable case. Anatomical evidence only.

Female child, aged twenty-five days. Mother died of catarrhal pneumonia. Autopsy of child showed in the middle of the right cerebellar hemisphere a caseating tubercle of the size of a hazel nut. The microscopical examination showed the appearance of caseating tubercle. No tuberculosis elsewhere. Doubtful.

States that in autopsies of infants dying during the first months of life he had often found tuberculosis of such advanced stage as to make a congenital origin very probable. He refers also to cases of "wirklich congenitaler Tuberculose" reported by Ancell, Langstaff, Husson, Chaussier, Dupuy, Andral, Lobstein, Scanzoni, Rilliet and Barthez, Charrin and Demme. All of these cases doubtful.

Tuberculous mother, aged seventeen years. Child died on the ninth day after birth. Autopsy showed two small cavities, filled with caseous material, in posterior margin of lower right lobe. Microscopical examination confirmed the gross diagnosis of tuberculosis. Very probable case. Anatomical evidence. (Berti reports a second very doubtful case which may be entirely ruled out.)

Two cases: (1) Child dying on twenty-first day. Autopsy showed advanced tuberculous ulceration of intestine. (2) Child dying on twenty-ninth day of pulmonary tuberculosis. Both cases very doubtful. History meager. Evidence anatomical only. Extra-uterine infection not excluded.

Female child of tuberculous mother, dying five weeks after delivery. Child ill for three weeks with cough and attacks of vomiting. No evidence of syphilis. Died in eighth week. Autopsy showed advanced caseous tubercles of lung, liver, spleen, and kidneys. Bronchial and mesenteric glands enlarged, but not caseated. Intestines not ulcerated. One tracheal gland caseated. Probable.

Female child, aged eleven weeks, of tuberculous mother. Autopsy showed extensive cavity formation in right lower lobe. Doubtful. Extra-uterine infection not excluded.

Three-months-old child, with extensive caseation and cavity formation. Mother healthy; father tuberculous. Very doubtful. Extra-uterine infection not excluded.

1880, DEMME (*Bericht über die Thätigkeit des Jennerschen Kindersp. in Bern*, 1880, No. 17).

1882, BAUMGARTEN (*Volkmann's Samml. klin. Vortr.*, 1882, No. 218).

1882, BERTI (*Bolletino delle Scienze med. Bologna*, 1882; cited by GÄRTNER).

1884, DEMME (*Verh. d. 63 Vers. deutsch. Naturf. u. Aerzte*, zu Freiburg i. B., 1884).

1885, MONEY (*Brit. Med. Jour.*, 1885, 1, 1257).

1886, DEMME (*Bericht über d. Thätigkeit d. Jennerschen Kindersp. in Bern*, No. 24).

1886, QUEYRAT (*Contribution à l'étude de la tuberculose du premier âge*, Paris, 1886, 80 pp.).

- 1886, FLESCH** (*Jahrbuch f. Kinderh.*, 1886, 25. Also *Pest. med.-chir. Presse*, Budapest, 1886, 22, 830). In eight cases out of five hundred autopsies on children in the early months of life tuberculous cavities (large or small) were found in lower lung lobes. Extra-uterine infection not excluded. Statement too inexact. Very doubtful. Evidence anatomical only.
- 1886, FROEBELIUS** (*Jahrbuch. f. Kinderh.*, 1886, N. F. 24, 47-72). Found in 16,581 autopsies of children under two years of age 416 cases of tuberculosis. One died on third day, one in second week, one in third week, three at about three and one-half weeks, fourteen in second month, 119 in third month. No detailed account of these cases.
- 1886, HOUTINEL** (*Thesis*, Paris, 1886). In 996 autopsies under second year, eighteen cases of tuberculosis; two dying in the first fourteen days after birth. No detailed account.
- 1887, LANNELONGUE** (*Verneuil*, 1). Out of 1,005 cases of surgical tuberculosis in children from one to fifteen years of age examined within two years, four cases observed which he regards as of undoubted congenital origin: one child, six weeks old, with classical signs of tuberculosis of knee existing from birth; one, one month old, tuberculous osteoarthritis fourteen days after birth; one, three weeks old, tuberculous abscesses in left tarsus and right malleolar regions; one, sixteen days old, tuberculous otitis. Regarded as impossible for extra-uterine infection. (In another child of two months, right-sided tuberculous epididymitis with fistula. Scrotal engorgement some days after birth. Few details given concerning parents. Doubtful.)
- 1888, HUGUENIN** (cited by *LEBKÜCHNER, Gaz. de Hôp.*, Paris, 1888, 61, 785-88). Two cases: one dying at the age of seven weeks of general tuberculosis; one of premature birth in the seventh month, with general tuberculosis and cavity formation in left apex. Doubtful. Evidence anatomical. No details.
- 1888, BOSSELUT** (*Contribution à l'étude de la méningite tuberculeuse chez les jeunes enfants âgés de moins de deux ans*, Par., 1888). In a large number of autopsies on children dying of tuberculosis, meningitis found in one aged fourteen days, in two aged three weeks, in one aged six weeks, and in four aged eight weeks. Evidence not conclusive. No details.
- 1890, RINDFLEISCH** (*Beicht. d. 63. Naturforscherversammlung*, in Bremen, 1890). Child eight days old, of mother in advanced florid tuberculosis developing during pregnancy. Died of caseous pneumonia. General tuberculosis. Large caseous nodules in liver. Probable case. Anatomical evidence only.
- 1892, SARWEY** (*Arch. f. Gyn.*, 1892, 43). Monster (cranioschisis) delayed delivery. Born in eleventh month. Mother apparently healthy. Father with cough and sputum. Child showed caseous and partly calcified nodules in upper cervical vertebrae. Guinea pigs inoculated. Three out of six developed tuberculosis after three months. Very doubtful. No tubercle bacilli at point of inoculation.



Stillborn monster (encephalocele). Caseation abscesses in three uppermost cervical vertebrae. No bacilli found. Evidence only anatomical. Details not given. Very doubtful.

(Observations of Parrot.) Child of eighteen days. Deep tuberculous ulcers in intestine. Caseation of tracheal and bronchial glands. Most probably congenital, as the extensive changes could hardly have occurred from extra-uterine infection.

Twenty-two other cases of tuberculosis in children under three months; one, four weeks old; one, five weeks (premature birth); two, six months; five, two months; eight, two and one-half months; five, two and three-quarter months. No details given. All doubtful cases. Purely clinical observations.

Child six weeks old with bronchial catarrh and otitis tuberculosa. Died four and one-half weeks later. Autopsy showed extensive tuberculosis of both lungs, diaphragm, liver, and kidneys, with advanced caseation. Wassermann believed case to be acquired from the relative of mother with whom the latter and child had resided for a short time when child was ten days old. Correctness of this opinion questioned by Baumgarten and Lebküchner. Very doubtful case.

Reports three cases, aged thirty-one days, thirty-eight days and sixteen weeks respectively, of combined tuberculosis and syphilis. Mother in first and third cases tuberculous. Autopsies of children showed advanced tuberculosis in all three cases. Tubercle bacilli present. Age of children and the fact that congenital syphilis predisposes to rapid development of tuberculosis make these cases doubtful.

Child three weeks old showed caseous tubercles in lung, spleen, bronchial, and mesenteric glands. Doubtful case. Full details not given.

Out of one thousand autopsies on children there was observed three times, in children of four, five, and six weeks, an intense tuberculosis of bronchial glands, which he regarded as congenital. No details given. Doubtful.

Mentions one case, dying on the twentieth day, of premature birth. Mother, suffering from advanced tuberculosis, died shortly after the child. On autopsy child found to have caseous bronchial glands, and miliary tuberculosis in lungs, none in liver, alimentary tract, or spleen. Regarded as probably congenital from advanced nature of lesions. Doubtful.

**1892, BAUMGARTEN U. ROLOFF** (*Arbeiten aus dem path.-anat. Institut zu Tübingen*, 1892).

**1892, LEROUX** (*La tuberculose du premier âge, d'après les observations inédites du prof. Parrot, Verneuil, Paris*, 1888).

**1894, WASSERMANN** (*Zeitschr. f. Hyg. u. Infektionskrankh.*, 1894, 17, 343-54).

**1894, HOCHSINGER** (*Wien. med. Bl.*, 1894, 17, 255-57).

**1895, STRAUS** ("La tuberculose et son bacille," *Rev. gén. de l'antisept. méd. et chir.*, 1895, 8, 97).

**1896, KISSEL** (*Arch. f. Kinderheilk.*, 1898, 25, 67).

**1896, HOLT** (*Med. News*, 1896, 69, 656-59).

- 1897, HENOCH** (*Vorles. über Kinderkrankh.*, Berlin, 1897). Father died of tuberculosis. Child ill from sixth week with multiple tuberculous abscesses over entire body. Died in fourth month of inanition. Autopsy showed advanced pulmonary tuberculosis, intestinal tuberculosis, and caseation of lymph glands. Very doubtful. Extra-uterine infection not excluded.
- 1898, BONNET** (*Lyon. Méd.*, 1898, 87, 224). Mother died of pulmonary tuberculosis two months after delivery. Male child, ill from birth, died at three months. Autopsy showed both lungs studded with caseous tubercles, tuberculous ulcers in ileum, caseous tuberculosis in mesenteric glands, kidneys, spleen, and liver. Fatty liver. Stage of lesions, and the fact of illness from birth, the child having been kept from danger of infection, given as reasons for regarding case probable.
- 1899, JOHNSON** (*Phil. Med. J.*, 1899, 3, 231) White female child born of mother with tuberculosis of bladder. At birth infant very weak, small; could not nurse. Emaciation increased. Made efforts at coughing. Died during a profuse pulmonary hemorrhage. Father healthy. Urine of mother contained blood, pus, and tubercle bacilli. Placenta probably tuberculous (see below). Autopsy of child showed extensive tuberculosis of right lung, pleura, and pericardium; miliary tuberculosis of left lung. Tubercle bacilli could not be found in fetal organs. Evidence not complete, but most probably a case of congenital tuberculosis.
- 1899, F. LEBKÜCHNER** (*Arbeit. aus dem path.-anat. Institut zu Tübingen*, 1899, 3). Two cases: (1) Mother of tuberculous family, suspicious symptoms, but case not certain. Child short of breath and coughed from birth. On section advanced tuberculosis in all organs. (2) Case similar, but child older. The first case may be regarded as probable, though evidence is incomplete.
- 1900, FRIEDMANN** (*Deutsch. med. Wchnschr.*, 1900, 26). Child twenty-six days old, with solitary tubercle in right apex. Not conclusive.
- 1900, LYLE** (*Phil. Med. J.*, 1900, 5, 219). Negress, twenty-two years of age, in seventh month of pregnancy, suffering from chronic pulmonary tuberculosis. Died two days after premature delivery. Autopsy showed chronic tuberculosis of both lungs and intestinal ulceration. Placenta appeared normal. Child apparently full-term; weighed about three pounds. Ill from birth; subnormal temperature for four weeks, followed by fever; died in eighteenth week. Autopsy revealed extensive tuberculosis of lungs, liver, spleen, and kidneys; tubercle bacilli present in the caseous areas. The great number of tubercles of same advanced stage, the fact that child was ill from birth and had been kept under such conditions as to exclude possibility of infection, are the reasons adduced for considering this case as congenital. It is doubtful, however, because of the long period (nineteen weeks) between birth and death.

## II. PLACENTAL TUBERCULOSIS.

## A. UNDOUBTED CASES.

(Diagnosis resting upon demonstration of both histological changes and the presence of tubercle bacilli in the placenta.)

CASE I.—Woman, aged twenty-six years, died of general miliary tuberculosis in seventh or eighth month of pregnancy. Male child removed by Caesarean section five minutes after death of mother; showed no signs of life. Well-developed. The only abnormal changes found were two grayish nodules in the right apex. Pieces of liver and spleen were inoculated into guinea pigs. General appearance of placenta was normal. In several places small miliary nodules, grayish, semi-translucent, and sharply outlined, were found. The microscopical examination of fetal liver and lungs gave no appearance of tuberculosis. No tubercle bacilli found. The placental nodules presented the appearance of typical caseating tubercles, containing few tubercle bacilli.

1893-94, LEHMANN  
(*Deutsch. med. Wchnschr.*, 1893, 19, 200-202).

CASE II.—Mother died of chronic tuberculosis of lungs and larynx. Child died ten days after birth. Presented no evidences of tuberculosis at autopsy. Typical caseating tubercles containing tubercle bacilli found in the placenta.

(*Berl. klin. Wchnschr.*, 1894, 31, 601).

CASE I.—Woman, aged twenty-six, in seventh or eighth month of pregnancy, died of chronic pulmonary tuberculosis and miliary tuberculosis. Child removed by Caesarean section; lived two hours. No histological changes of tuberculosis or tubercle bacilli found in fetus. Placenta appeared normal to the naked eye. Numerous tubercle bacilli found in smears from placenta. Animal inoculations negative. On microscopical examination placenta showed typical tubercles in all stages. Tubercle bacilli in large numbers.

1894, SCHMORL-KOCKEL  
(*Ziegler's Beiträge*, 16 313).

CASE II.—Mother, aged twenty-five, died of general miliary tuberculosis. Fetus removed at autopsy. No evidences of tuberculosis in fetal organs. Tubercle bacilli found in fetal liver. Periportal tissue and lymph glands without anatomical changes. Animal inoculations negative. Typical tubercles containing tubercle bacilli found in placenta.

CASE III.—Woman, aged thirty-three, died in ninth month of pregnancy of chronic pulmonary tuberculosis. Child removed by Caesarean section; dead when uterus was opened. Male child, showing no changes of tuberculosis. No tubercle bacilli found in fetal tissues. Placenta presented no naked-eye appearances of tuberculosis. Animal inoculations with fetal tissue negative.

Microscopically the placenta showed typical tubercles in varying stages, not so numerous as in Cases I and II. Tubercle bacilli present in large numbers.

1896, WARTHIN, (*Med. News*, 1896, 69, 319-24.)

Case of tubal gestation with tuberculosis of tubes, placenta, and fetus. Rupture of tubal sac in fourth month; operation. Advanced tuberculosis of tubes, and wall of sac. Chorionic villi involved directly by extension from wall of tube. Typical tubercles in chorionic villi. Few tubercle bacilli found.

1898, AUCHÉ AND CHAMBRELENTE (*Munch. med. Wechnschr.*, 45, 1898, 616).

Mother, far advanced in tuberculosis, died three days after premature delivery in seventh month. Placenta showed numerous caseous tubercles containing tubercle bacilli. Inoculation of guinea pig positive. Child lived twenty-six days. Autopsy showed extensive tuberculosis.

1899, WARTHIN ("Unusual Localizations of Tuberculosis," *Medical News*, 1899).

In one of fifty successive placentas examined at the Stadt-Krankenhaus in Dresden (Schmorl's Laboratory) miliary tubercles in all stages were found in full-term placenta. Contained few bacilli. Nothing known of mother or child, as placenta could not be identified.

#### B. PROBABLE CASE.

1899, JOHNSON (*Phil. Med. J.*, 1899, 4, 930).

Mother had tuberculosis of bladder. Child lived a little over three months. Ill from birth. Autopsy showed extensive and old tuberculous lesions. Placenta contained necrotic areas. On microscopical examination areas of necrosis, diffuse inflammation, and foci of coagulation necrosis were found. No giant-cells and no tubercle bacilli. The character of the changes, as shown by the figure given, makes it probable that the placental lesions were tuberculous.

### III. TUBERCLE BACILLI IN FETUS AND PLACENTA WITHOUT HISTOLOGICAL CHANGES.

#### A. UNDOUBTED CASES.

(Diagnosis resting upon the demonstration of the bacilli by staining or by inoculation of animals.)

1883, LANDOUZY AND MARTIN (*Rev. de Méd.*, 1883, 3).

A portion of the lung of the six and one-half months' fetus of a tuberculous mother, dying a few days after delivery, was inoculated into the peritoneal cavity of guinea pigs. Animals died of general tuberculosis four months afterward.

1885, KARTH AND CHARIN (*ibid.*, 1885, 5, 659-72, cited by FRIEDMANN).

Guinea pig inoculated with portion of placenta from tuberculous mother. Result positive.

1891, HERRGOTT AND HAUSHALTER (*Ann. de Gyn. et d'Obst.*, 1891, 36, 1, 100).

Woman dying of chronic pulmonary tuberculosis in sixth month of pregnancy. Inoculation of guinea pigs with amniotic fluid positive. The only case of the kind recorded.

Seven-month fetus extracted by Caesarean section from mother, twenty-three years of age, dying of miliary tuberculosis. Tubercle bacilli found in fetal liver, in intervillous spaces, and in chorionic villi. No histological changes of tuberculosis found. Inoculation of guinea pigs with portions of fetal liver were positive in three cases.

Two cases: (1) The seven-month fetus of a tuberculous mother showed no histological changes. Inoculation of guinea pig with portions of fetal organs gave positive results. (2) The five-month fetus of mother dying of tuberculosis presented no histological changes. Placenta apparently normal. Inoculations with portions of placenta and heart-blood of fetus were positive; inoculations with fetal liver doubtful; inoculations with portions of lung and brain were negative.

The seven-month fetus of mother dying of acute miliary tuberculosis showed no histological changes. Bacilli in fetal blood. Inoculation of guinea pig with portions of placenta and fetus gave positive results. Case like the one of Schmorl and Birch-Hirschfeld.

Mother died of pulmonary and intestinal tuberculosis fourteen days after delivery. Child died on fourth day. Numerous tubercle bacilli were found in fetal liver, spleen, and kidneys. No histological changes found. Inoculations of guinea pigs with blood from umbilical cord positive.

Two cases: (1) Mother died of acute miliary tuberculosis eight days after abortion. No tuberculous changes or tubercle bacilli found in fetus. Inoculations of guinea pigs with portions of liver and placenta, and with fetal blood, were positive. (2) Mother with advanced tuberculosis. Child died ten days after birth. No tuberculous changes or tubercle bacilli found in fetus. Inoculations with venous blood, portions of fetal organs, and placenta were positive.

Three cases of abortion in mothers suffering from general tuberculosis. No histological changes found in fetus in any one of the cases. In only one case tubercle bacilli were found in the fetal liver, periportal tissue, and lymph glands. The placenta in each case contained bacilli and tubercles. The inoculation with portions of fetal organs was negative in all three cases.

Portions of the placentas and fetal organs from six mothers suffering with chronic pulmonary tuberculosis were inoculated into animals, with positive results in four cases. In one case tubercle bacilli were found in great numbers in the fetal organs.

1891, SCHMORL AND BIRCH-HIRSCHFELD (*Beiträg. z. path. Anal. u. z. allg. Path.*, 1891, 9, 423-39).

1891, LANDOUZY (*Rev. de Méd.*, 1891, 11, 411, 431).

1892, AVIRAGNET (*Union Méd.*, 1892).

1893, THIERCELIN AND LONDE (*Méd. mod.*, 1893, 4, 398).

1893, LONDE (*Rev. de la Tuberc.*, 1893, 125-43).

1894, SCHMORL AND KOCKEL (*Ziegler Beiträge*, 1894, 16).

1895, LONDE (*Compt. rendus Acad. de Sci.*, 1895, 121, 544).

1896, BUGGE (*Ziegler Beiträge*, 1896, 19).

Eight-month fetus of mother with miliary tuberculosis lived but thirty hours after birth. Mother died shortly afterward. Tubercle bacilli were found in the blood from the umbilical vein and in the liver vessels. No histological changes found. Three guinea pigs inoculated with blood from the umbilical vein. Portions of fetal liver and lung gave positive results.

1896, DOLÉRIIS AND BOURGES (*Semaine méd.*, 1896, 375).

Mother died of acute miliary tuberculosis three weeks after delivery of a seven-month child. The marasmic infant died five weeks after birth. No tubercle bacilli or histological changes of tuberculosis found in child. The inoculation of a guinea pig with the heart-blood of the child gave positive result of special interest, in that the child should contain bacilli for five weeks without occurrence of tissue changes. Case doubted by Hauser and Cornet for this reason.

#### B. DOUBTFUL CASES.

(Regarded as doubtful because of meagerness of details, length of time elapsing after inoculation, lack of control experiments, etc.)

1883, LANDOUZY AND MARTIN (*Rev. de méd.*, 1883).

Mother died of tuberculosis in fifth month of pregnancy. Portions of the placenta and twenty to twenty-five drops of fetal heart's blood inoculated into three guinea pigs. All died of general tuberculosis four months afterward. Three guinea pigs inoculated with portions of fetal liver, lung, and brain remained alive.

1890, ARMANNI (*X. Internat. Med. Cong. in Berlin*, 1890).

Mother died of tuberculosis in seventh or eighth month of pregnancy. Fetus showed no histological changes. Portions of spleen, liver, and brain were inoculated into two guinea pigs. One died four months afterward of general tuberculosis; the other not affected. Secondary infection of pig not excluded.

1893, THIERCELIN AND LONDE (*Méd. mod.*, 1893, 4, 398).

Mother died fourteen days after delivery. Had pulmonary and intestinal tuberculosis. Child died a few days after birth. No autopsy. Portion of placenta placed in peritoneal cavity of guinea pig gave positive result. Actual condition of child not known.

1893, LONDE (*Rev. de la tuberc.*, 1893, 125-43).

Mother died of tuberculosis ten days after delivery. Age of child not given. No autopsy. Inoculation of guinea pig with portion of placenta positive.

1895, BAR AND RENÓN, (*Annal. de Gyn. et d'Obst.*, 1895, 41, 43, 44; see also *Sem. méd.*, 1895).

Five cases of delivery of tuberculous mothers. The blood of umbilical vein was injected immediately into guinea pigs. Three cases gave negative results; two were positive. Of the latter one case showed no apparent lesions in placenta or fetus. No bacilli found. Mother had late stage of pulmonary tuberculosis. Three animals were inoculated with pieces of liver and

lung and with peritoneal fluid. The one inoculated with portion of liver had local lesion and general tuberculosis; the one inoculated with peritoneal fluid had tuberculosis of spleen, but no local lesion.

The second case is very doubtful, secondary infection not being excluded. Mother had tuberculous cavities in lungs. Child died of bronchopneumonia on the fortieth day after birth. Placenta appeared normal. Two guinea pigs were inoculated with blood from umbilical vein; one negative; the other developed local and general tuberculosis.

The placentas of thirteen tuberculous mothers, and in a few cases portions of the fetus also, were examined for tubercle bacilli. These were found once in the maternal blood. In eight cases in which the fetus was examined histologically and animals inoculated, no histological changes were found. In only one case the inoculation with placenta was positive. Report inexact and contradictory.

Mother had chronic tuberculosis. Child died four days after delivery. Autopsy showed pneumonia with fresh fibrinous pleuritis. No microscopic changes of tuberculosis. Portions of an apparently healthy bronchial gland were inoculated into guinea pig. Pig showed general tuberculosis on the thirty-seventh day. Neither histological changes nor tubercle bacilli could be found in serial sections of another gland. Author excludes accidental infection of inoculated animal and regards case as a typical tuberculosis inoculation. No control of experiment. Secondary infection of wound not excluded.

**1895, BOLOGNESI** (Thesis, Paris, 1895.)

**1896, HENKE** (*Arbeit aus dem path.-anat. Instit. z. Tübingen*, 1896, 2.)

A number of investigators have also examined the fetus and placenta of tuberculous mothers for tubercle bacilli and evidences of tuberculosis, but without positive results. Leyden, Wolff, Houtinel, Vignal, Londe, Grancher and Straus, Bar and Renón, Bugge, Borst, Heinemann, and others have examined fetal and placental tissues for tubercle bacilli, by staining and inoculation of animals, with negative results. On the other hand, such investigation has been carried out in cattle by a large number of veterinarians with positive results. To these (Johne, 1885) we owe the first positive proof of the intra-uterine transmission of tubercle bacilli.

The above synopsis of the literature shows, therefore, a paucity

of thoroughly studied cases bearing upon the important question of human placental and congenital tuberculosis. The completeness of the study which we have been able to give one case makes it of especial value at this time.

#### HISTORY OF CASE.

Mrs. H. M., aged twenty-seven, was seen in consultation with Dr. Neil Gates, of Dexter, Mich., Oct. 17, 1901.

The patient complained of frequent and painful micturition, great weakness, sweating, and cough.

Father, brother, and three aunts died with pulmonary tuberculosis.

Patient has been married between three and four years. Has one child living and in apparent perfect health. She has always done housework. She was born in Colorado, and was always sickly as a child. At the age of two weeks she had "a severe cold in the head, stopping of the nose, and croupy cough." These symptoms lasted for about one week, and were followed by "breaking and discharge" from both ears. Soon after the beginning of the ear symptoms she was brought from Colorado to Michigan, when her nose began to discharge a thick, yellowish, creamy substance in abundance, having an offensive odor and similar to the discharge from the ears. The left ear discharged more than the right. The hearing has been impaired ever since. An out-of-door life resulted in a moderately quick recovery from the acute symptoms. A chronic discharge from both ears, however, persisted.

Except that she was troubled with a frequent desire to urinate, which was a noticeable symptom, she was well, but frail, for the remainder of her childhood.

Patient began to menstruate at the age of fourteen, with little or no pain. For a year or more prior to present pregnancy, menses have been irregular, at one time skipping two months. The flow was profuse, at times lasting six or seven days. No miscarriages.

Seven years ago micturition began to be more frequent, producing a burning sensation, and at times causing actual pain. She sought relief in many ways, but was unsuccessful. After her marriage, a little over three years ago, these symptoms grew worse, and since that time it has been necessary for her to urinate every half-hour, sometimes every fifteen minutes. This was especially noticeable if she rode in a carriage. When going to town, a thirty-minute drive, she was obliged to get out of the carriage two and sometimes three times. The amount of urine at each micturition was small, and toward the last amounted to only 3 or 4 c.c. For the last six months she has urinated every half-hour through the night. At no time did these symptoms abate. They grew steadily worse. Neither her husband nor her mother ever noticed any blood in patient's urine excepting during menstruation. She never complained of her feet or her legs swelling, nor was this symptom ever noticed by her husband, mother, or her physician, who saw her frequently for three years.

She had a chronic cough for a year or two, expectoration always being



scant. During the past summer her cough was dry and distressing, and was unrelieved by taking medicine. She has had attacks of sweating until present illness began.

*Present illness.*—On Thursday, October 3, 1901, patient went to a county fair. The day was cold. She was dressed in light summer clothes. When she reached home, after a drive of four miles, she complained of being very cold. Her lips were purple. The next day she began to cough very hard. On Sunday, October 6, she had a fever, and Dr. Gates was summoned. Her temperature, at this time, “was 102° F., and her pulse weak and rapid.” She was put to bed, and soon after this she had a distinct chill; her temperature rose higher, and she complained of her throat being sore. From this time until the patient was seen by Dr. Cowie her temperature ranged from normal to 100° F. in the morning, to from 101° to 103° in the evening.

She was first seen by Dr. Cowie on the afternoon of October 17, 1901, two weeks after she was taken ill. She looked very weak and tired. She was sweating profusely all over, more markedly on the forehead. Her eyes were bright, her cheeks flushed, and her respiration quick and shallow. The appearance of her face was like that of croupous pneumonia. Her speech was slow. She suffered much pain from micturition, which now occurred every five or ten minutes. Her temperature was 101°, pulse 110 and fairly strong, respiration about 40. She was in about the fifth (?) month of pregnancy.

#### PHYSICAL EXAMINATION.

(October 17, 1901.)

The patient is emaciated; musculature is small and wasted. All of the ribs are visible. The skin is slightly sallow, except over the face where it is flushed. The panniculus is very thin. There are lineae albicantiae over the lower part of the abdomen, and a distinct linea fusca below the umbilicus. There is no edema. The hearing is impaired in both ears. She has a dry cough, but no expectoration. Lies in active dorsal position.

The thorax is long; the epigastric angle is narrow. The breathing is quick, shallow, and labored, the accessory muscles being brought into use. The expansion is slight.

*Palpation.*—The vocal fremitus is increased on both sides, particularly over the upper left lobe.

*Percussion.*—There is impaired resonance over the upper right lobe, while the percussion over the corresponding area on the left elicits a dullness having in it a slight resonant quality. The note is distinctly higher and its quality duller than that obtained on the right side. Over the back the area of impaired resonance is more extensive. On the left it extends to the lower border of the scapula; on the right, over the upper third of the scapula; below this line the resonance approaches more closely that of a normal lung. Apices and lower lung borders were not noted at the time.

*Ausculation.*—Inspiration is short and jerky; expiration is short, but is slightly longer than inspiration and is followed by a short pause. Over the left upper lobe the breathing is blowing, and a number of fine crackling subcrepitant râles are heard, occasionally a dry piping râle. No moist râles.

Over the upper right lobe there is increased vesicular breathing. Blowing breathing is heard on this side only over a small area two fingers to the right of the sternum in the second intercostal space. There are no râles below or above the clavicle, except an occasional crackling one. No friction sounds are heard.

The examination of the heart is negative.

*Abdomen.*—The abdomen is markedly above the level of ribs. Pregnancy about fifth month (?). Fetal movements and heart-beat present. Further examination unsatisfactory.

No sputum could be obtained. Patient was too weak to expectorate and swallowed the little she raised. No microscopic examination was made, because no sputum could be obtained. Her sputum had never been examined for tubercle bacilli.

Urine was obtained per catheter under sterile conditions in a sterile bottle, but by mistake the bottle was thrown out by one of the family. Large numbers of tubercle bacilli were found in the urine obtained from the bladder at autopsy (see autopsy record). (During last two years her urine had been examined chemically a number of times; albumin was a constant constituent. No microscopic examination was made.)

A diagnosis of acute miliary tuberculosis was given as the result of the consultation.

Dr. Cowie did not see the patient again until Monday, October 21, when the case appeared to be approaching rapidly a fatal issue. The fetal movements and heart-beat were absent. Relief from painful micturition was secured by the use of a sterilized soft rubber catheter retained in position.

As was expected, she aborted early on the following morning. The fetus gave no evidence of life. The fetus and membranes, placenta and cord, were taken to the pathological laboratory almost immediately after the abortion. The patient died on the same day, about twelve hours later. Through the efforts of Dr. Gates an autopsy was secured. This was performed by Dr. Warthin, at 11 A.M., October 23, 1901, at patient's home in the country. Measurements and weights could not under the circumstances be obtained.

#### AUTOPSY PROTOCOL.

Cadaver of slender build. No anomalies or deformities. Abdomen greatly distended. Muscles small, greatly emaciated. Rigor mortis present throughout. Very small amount of panniculus. Slight edema over ankles. Body heat absent. Skin slightly sallow; faint linea fusca below the umbilicus. Very slightly marked linea albicantiae over the lower portion of abdomen. Moderate hypostasis over back. Post-mortem percussion gave dulness over both lungs, more marked over the left.

*Brain and spinal cord* were not examined.

No fluid in peritoneal cavity; peritoneal surfaces dry and sticky. Transverse colon enormously distended, lying in a downward curve extending below the level of the umbilicus. Ascending colon slightly distended; the descending also, as far as the sigmoid, is greatly distended. Pelvis filled with the enlarged and contracted uterus. Otherwise the position of abdominal organs is negative.

*Diaphragm* at fourth intercostal space on right, fifth rib on left.

*Mammae* small; areolae pale. A small amount of colostrum can be expressed from the nipples. On section the acini are hyperplastic, the ducts enlarged and filled with a yellowish viscid fluid.

Examination of *mediastinum* negative. No remains of *thymus*. The *lungs* are voluminous, completely covering the small heart. Apex in fourth intercostal space just outside the left parasternal line. No fluid in pleural cavities. Pleural surfaces cloudy. No adhesion on right; over the apex and base of the left lung there are old firm adhesions.

*Pericardial fluid* slightly increased and slightly cloudy; subepicardial fat somewhat increased. Parietal pericardium negative; a few remains of old adhesions over the visceral layer. Heart small, size of cadaver's right fist. Ventricles filled with cruor. Right auricle contains large, white, ante-mortem jelly clot. Walls of normal thickness; fat slightly increased. Heart muscle firm. Valvular orifices and flaps negative. No tubercles in heart or pericardium.

The *left lung* is moderately voluminous, firm and inelastic, especially over the lower lobe, where it is almost airless. The pleura of lower lobe is cloudy and covered with small pin-point nodules which on section are firm, semi-translucent, and showing caseous centers. The cut surface is bluish-red, bleeds freely; it is studded with countless small, grayish, pin-point nodules, some of the largest showing caseation.

The *right lung* is voluminous, of much lighter color, particularly the upper and middle lobes, which are pink, the lower one red. Beneath the pleura there are everywhere small pin-point nodules, somewhat smaller than those of the left lung. Beneath the pleura on the anterior surface of the lower lobe there are several flattened tubercles size of a pea and deeply pigmented. On section the centers show grayish caseation. The section of the right lung is similar to that of the left, showing countless miliary tubercles about the size of a pin-head, very few being caseous.

Ante-mortem white clots are present in pulmonary veins; red clots in the arteries. The *bronchi* contain a large amount of frothy sputum; their mucosa is deeply injected. The *bronchial glands* are enlarged; softened, moderately anthracosed, and contain a few miliary tubercles. Careful examination of the *thoracic duct* shows no involvement by the tuberculous process. The examination of *esophagus* and *thoracic vessels* is also negative.

The examination of *nose*, *tonsils*, *pharynx*, *larynx*, *trachea*, *cervical vessels*, and *nerves* is negative. The thyroid is slightly enlarged, on section negative. Parathyroids negative. No tuberculous process found in *cervical lymph glands*.

The *spleen* is a little over twice as large as normal; its capsule slightly thickened. Consistency very soft. Organ is flattened. There are two shallow notches on the anterior surface, and one deep one on the posterior edge. On section the cut surface is deep bluish-red. Scattered throughout the pulp are numerous miliary nodules, hard and semitranslucent, none showing caseation.

The examination of the *adrenals* is negative. No tuberculosis.

The *left kidney* is enlarged. The fatty capsule is rich in fat; the fibrous

capsule is adherent. On section the medullary pyramids are found to be almost entirely destroyed, and replaced by tuberculous abscesses showing advanced caseation and liquefaction. The abscess cavities are filled partly with caseous material and partly with a thin cloudy fluid. They are encapsulated, the capsule consisting of a dense, firm, hyaline layer of connective tissue. The pelvis is greatly dilated; its mucosa thickened and ulcerated, presenting numerous caseating nodular masses. The cortex is very pale, semitranslucent, and firm. The outlines between labyrinth and medullary rays almost entirely lost. Miliary tubercles are scattered throughout the cortex.

The *right kidney* is much smaller than the left. There are encapsulated tuberculous abscesses in the pyramids. Otherwise the appearance is similar to that of the left.

The *ureters* are dilated, their mucosae thickened. They contain cloudy urine and caseous material. The *bladder* contains two tablespoonfuls of thick cloudy fluid. The mucosa is thickened, covered with fibrin flakes and cheesy material, and presenting small erosions or ulcerations.

The examination of the *stomach, large and small intestines, appendix, and rectum* is negative, with the exception of the distention noted above.

The *liver* is much enlarged; capsule negative. On section the cut surface shows a moderate nutmeg appearance. No tubercles visible to the naked eye. The *gall-bladder* contains a small amount of bile; no stones are present. The examination of the *portal vein* is negative.

The *external labia* are edematous and purplish-red in color. The vagina is dilated; its mucosa deeply congested and covered with a bloody discharge. The examination of the urethra is negative. The uterus is the size of a large cocoanut; presents the appearance of a post-partum organ. It is firmly contracted and lies deep in the pelvis. Cervix is dilated; no laceration. Uterine vessels greatly congested. *Placental site* in upper right anterior portion of fundus. Some placental tissue *in situ* covered with large blood-clots. Entire endometrium covered with decidual shreds and large clots. On section the decidua at the placental site shows thrombosed sinuses. No evidences of tuberculous processes visible to naked eye.

No pathological changes in the *tubes* or *ovaries* apparent to the naked eye. True corpus luteum in left ovary. The blood-vessels of the broad ligament are enormously congested.

The examination of *bones, joints, and other peripheral structures* is negative.

Portions of all organs were fixed in formalin, mercuric chloride, and alcohol; imbedded in paraffin, and stained with ordinary stains. Specific stains for tubercle bacilli (carbol fuchsin) and fibrin (Weigert's) were also employed.

#### MICROSCOPICAL.

*Lungs*.—Sections taken from different portions of both lungs show a general miliary tuberculosis of both organs. The majority of the tubercles are in a stage of advanced caseation, many of them showing much formation of reticulum and beginning encapsulation. Giant cells are present in large numbers in the majority. In many of the larger branches of both pulmonary

arteries and veins miliary tubercles are found projecting into the lumen of the vessel and apparently arising from the wall of the vessel (hematogenous metastasis). Tubercle bacilli are found in abundance in the caseating nodules. The advanced caseation, the abundant reticulum, and the attempt at encapsulation seen in many of the tubercles justify the diagnosis of sub-acute miliary tuberculosis. The sections show further a marked congestion, edema, and extensive pneumonia.

*Bronchial glands.*—Scattered miliary tubercles of same stage of development as those in the lungs.

*Heart muscle.*—Slight atrophy and fatty degeneration. Slight fatty infiltration beneath epicardium. No tubercles found in heart.

*Spleen.*—Numerous miliary tubercles scattered throughout pulp, of same stage of development as those in lungs. Marked congestion. Coagulation necrosis of some of the follicles.

*Adrenals.*—Negative, post-mortem change of medullary portion.

*Kidneys.*—The large abscesses in the medullary pyramids are tuberculous; the abscess cavity filled with caseating material; the wall of the abscess composed of epithelioid tissue containing numerous giant cells. There is also a distinct capsule formation about the largest abscesses. The medullary structure between the tubercles is for the greater part destroyed. The cortical portion presents the appearance of a primary interstitial nephritis. Scattered throughout the cortex are numerous miliary tubercles of various stages of development. The pelvis shows an advanced stage of tuberculosis. The largest branches of the renal vein are involved in the tuberculous process. The advanced stage of the lesions in the kidneys justifies the diagnosis of chronic tuberculosis of the kidney, with resulting secondary interstitial nephritis.

*Liver.*—Countless miliary tubercles occur in sections taken from all parts of the organ. They are for the greater part of smaller size than those of the lung, but show also advanced caseation, reticular formation, and in some instances encapsulation. Giant cells are numerous. There are also many small epithelioid tubercles without caseation. The other changes found are those of moderate chronic passive congestion (nutmeg liver).

*Pancreas, stomach, and intestines.*—Negative.

*Ovaries.*—In the left ovary there is present, just beneath the surface, a corpus luteum of oval shape, measuring  $1 \times 1$  cm. The lutein cells are atrophic and vacuolated. The protoplasm of many is fragmented, and the nucleus does not stain. Within the corpus luteum there are scattered miliary epithelioid nodules showing caseation and numerous giant cells. In one portion several confluent tubercles occur, and these show abundant reticulum and beginning encapsulation. The lutein cells immediately about the tubercles are vacuolated or necrotic. With the exception of two small epithelioid tubercles containing giant cells, but not showing caseation, no tubercles were found in other portions of the left ovary or in any portion of the right. No other pathological changes were found in either ovary.

*Tubes.*—Negative; no tubercles found.

*Uterus.*—Uterine wall shows the characteristic changes of the pregnant uterus. No tubercles found in wall. Endometrium gives the appearances of

post-partum decidua at full term. No tubercles found in decidua. In the decidual and subplacental sinuses there are numerous hyaline thrombi characterized by the presence of leucocytes, the nuclei of which are undergoing disintegration. The chromatin of the nuclei is broken into small granules, or in other cases it is represented by diffuse blue staining. The thrombi are composed partly of fibrin and partly of fused red cells (agglutination thrombi). Tubercle bacilli are found in great numbers in these thrombi, and they also lie scattered among the red cells in the placental and decidual sinuses. At the points where the thrombi are adherent to the wall of sinus or vessel slight changes may be found in the wall, either of the nature of a necrosis or beginning epithelioid proliferation, with an occasional characteristic giant cell. No caseating tubercles were found. In some of the larger thrombi the central portion of the hyaline substance shows beginning liquefaction. The majority of the thrombi containing tubercle bacilli, however, present no appearances with ordinary stains that would distinguish them from the hyaline clots and thrombi found in the decidual sinuses under normal conditions, unless it be the almost universal occurrence of a diffuse chromatin-staining in their central portions.

*Bladder.*—Tuberculous cystitis.

#### BACTERIOLOGICAL EXAMINATION.

Tubercle bacilli were found in great numbers in the urine taken from the bladder at autopsy, in the caseous material from the kidney, and in the tubercles found in the lung and liver, and in the thrombi of the uterine and decidual sinuses. No bacilli found free in the blood in the vessels in any organ except in the uterus.

#### PATHOLOGICAL DIAGNOSIS.

Chronic primary tuberculosis of the kidneys; subacute miliary tuberculosis of lungs, liver, and spleen; tuberculous cystitis; tuberculosis of corpus luteum verum; tuberculous thrombosis of decidua; general marasmus; abortion.

#### FETUS.

(The fetus and placenta were brought to the pathological laboratory as soon as possible after the abortion.)

*Male fetus*, 25 cm. long, weight about 250 g., attached to middle of placenta by cord 30 cm. long and 5 mm. in diameter. Near the middle of the cord there are several small nodular thickenings. On section these present no pathological changes. The genital organs are perfectly formed. The finger and toe nails are perfect. The head is covered with a fine down; no down on body. The shoulder breadth is 9 cm.; the trochanter distance 4 cm.; circumference of cranium 20 cm. On section the right testis was found in the inguinal canal, the left one just above the internal ring. Careful examination of all the internal organs revealed no macroscopic evidences of tuber-

culosis or other abnormality. The age of the fetus was placed in the late sixth or early seventh month.

About one hundred blood-smears were made from the fetal blood of heart, hepatic vessels, spleen, and umbilical vein. A young and healthy guinea pig was inoculated with a beef-tea suspension of the fetal liver. All of the internal organs were fixed in mercuric chloride, imbedded in paraffin, stained with hematoxylin and eosin for histological study, and with carbol-fuchsin and methylene blue for the presence of tubercle bacilli. Weigert's fibrin stain and other methods were also employed in the study of the thrombi found in the blood-vessels.

#### MICROSCOPICAL EXAMINATION.

The careful search of sections taken from all the fetal organs failed to reveal any change of structure suggesting tuberculosis. The only pathological changes found were a few small thrombi in the interlobular vessels of the liver. These were hyaline in character, staining deep-red with eosin, and containing but few leucocytes. No necrobiotic changes were observed in the latter. The hyaline material forming the thrombi gave the fibrin reactions only in part, the remaining portion appearing to consist of agglutinated red blood-cells. Staining with carbol-fuchsin showed the presence of tubercle bacilli in the thrombi and also free in the hepatic vessels. No evidences of degeneration or proliferation of the cells of the blood-vessel or tissues in the neighborhood of the thrombi could be found. Staining of the blood-smears made from the fetal liver showed the presence of bacilli in one out of twenty smears. In the blood-smears stained with hematoxylin and eosin the number of megaloblasts and polychromatophile cells seemed greatly increased in numbers as compared with blood-smears taken from another fetus of about the same age.

#### BACTERIOLOGICAL.

A young and healthy guinea pig was inoculated with a beef-tea suspension of fetal liver on October 22, 1901. The animal showed an increase of temperature and began to lose weight in the second week after the inoculation. The loss of weight and fever continued steadily, and by December 2, the pig appeared very ill; would not move from corner of cage. It was chloroformed and examined immediately after death. Small caseating nodules were found at point of inoculation. In the posterior peritoneal wall there were a number of white nodules of the size of a pin-head. The omentum was rolled up, greatly thickened, and on section showed a cut surface studded with numerous miliary nodules, many of which presented yellowish, softened centers. The mesenteric glands were enlarged, but showed no macroscopic evidences of tuberculosis. The liver, lungs, and spleen were studded with innumerable grayish or yellowish pinhead nodules, many showing a central caseation. Scattered nodules similar to these were also present in the kidneys. The staining of smears made from some of the caseating nodules showed the presence of numerous tubercle bacilli. The microscopical examination of sections of omentum, liver, lungs, spleen, and

kidneys showed the nodules to present the characteristic appearances of miliary tubercles in varying stages of caseation. Staining of the sections with carbol-fuchsin likewise showed the presence of tubercle bacilli in these lesions.

A second pig was inoculated with a beef-tea suspension of the liver of pig No. 1 on December 2. On the next day the animal showed an increase of temperature, and from this time gradually lost weight. On December 18 it gave birth to two young ones. Three days afterward both mother and young died. Autopsy of mother showed a marked generally miliary tuberculosis. This was confirmed by microscopic examination and by the inoculation of a third pig. Other pigs were inoculated with beef-tea suspension of the livers of the two young of pig No. 2. The inoculated animals remained in perfect health months afterwards. No evidences of tuberculosis found in the organs of young.

#### PATHOLOGICAL DIAGNOSIS.

Bacteriemia (tubercle bacilli) of fetal blood, and agglutination thrombosis without histological changes of tuberculosis.

#### PLACENTA.

Placenta nearly round, disk-shaped, about 15 cm. in diameter and 3 cm. thick. Cord attached to middle. Naked-eye inspection showed nothing that with certainty could be regarded as pathological. Whitish and yellowish areas, varying in size from a pinhead to that of a cherry, were found on the cut surface, but in every way resembled the small anemic infarcts found in the normal placenta. The organ was cut into parallel strips about 5 mm. in breadth. Half of these were fixed in mercuric chloride and half in 4 per cent. formalin. When after-hardened in alcohol the placental tissue appeared thickly strewn with small grayish spots. The entire organ was imbedded in paraffin. Sections were taken from each block, and many of the latter were wholly cut up into serial sections. Ordinary stains—carbol-fuchsin, Weigert's fibrin stain, polychrome methylene blue, kresyl violet, tri-acid stain, etc., were used in the study of the sections.

#### MICROSCOPICAL EXAMINATION.

*Cord.*—Sections showed no histological changes of tuberculosis.

*Intervillous spaces.*—On examining the sections of the placenta stained with hematoxylin and eosin one is immediately struck by the presence in the intervillous spaces of small, round, hyaline, red-staining masses of a fibrogranular or nearly homogeneous structure, and containing a varying number of leucocytes. They vary in size, but the majority are of about the same dimensions. As seen in the mounted specimen, when held against the light, they are about the size of a small pinhead. In general they resemble the masses of fibrin found in the intervillous spaces of every normal placenta, but at once attract attention by their more regular outline, and by the fact that in nearly every one the leucocytes in the central portion of the mass show a marked karyorrhexis, the disintegration and diffusion of their chromatin



giving a bluish or violet stain to the center of the mass. Closer inspection shows also that many of these small masses contain characteristic giant cells with peripherally arranged nuclei. These giant cells do not resemble the syncytial buds or offshoots; serial sections show that most of them lie in the central part of the hyaline and fibrogranular masses, and are not connected with the villi. In the central portion of the larger masses there is a more finely granular appearance, resembling caseation. The giant cells in some instances are involved in this central disintegration. About the border of the masses the leucocytes stain better, the outlines of their nuclei being preserved.

In the great majority of the smaller masses no cells of epithelioid or fibroblastic type are found. The only elements constituting the mass are: (1) a groundwork of a hyaline, lumpy, or fibrogranular substance staining red with eosin; (2) in the meshes of this, leucocytes showing more or less karyorrhexis; (3) occasional giant cells with peripherally arranged nuclei, in all respects resembling the characteristic giant cells of tuberculous processes. With eosin the ground substance of these masses resembles fibrin; with Weigert's fibrin stain the greater part of it does not stain like fibrin. It stains with various methods as red blood-cells do; and in many cases a direct transition can be seen from red cells forming the periphery of the mass into the hyaline, lumpy substance forming the central portion. The general appearances and the staining reactions of this substance are the same as those of hyaline thrombi composed of red cells; and they correspond in all respects to the agglutination-thrombi described by Flexner.

Staining with carbol-fuchsin and methylene blue shows the presence of varying numbers of tubercle bacilli in all of these thrombi. Free bacilli are also found in the blood of the intervillous spaces.

The agglutination thrombi in some instances lie directly upon the syncytium of the villi, which does not show any perceptible changes. In other cases the syncytial covering of the villus is partly absent, and the thrombus rests directly upon the stroma of the villus. In these cases a proliferation of the cells of the stroma has taken place, and cells of a fibroplastic or epithelioid type have penetrated into the thrombus mass. The appearances are therefore more like those of an epithelioid tubercle. In several instances giant cells of characteristic type are found in the stroma of the villus, apparently arising *in situ*. In many places the syncytium not only does not seem to be affected by the proximity of the tuberculous thrombus, but has evidently extended over and partly surrounded the mass attached to the villus.

Larger areas of thrombosis are found filling up the spaces between a number of villi, the latter showing necrosis. The appearances are similar to those of an ordinary placental infarct, except for the central caseation and the presence of giant cells unlike those of the syncytium. Occasional large areas are found resembling caseous necrosis. Outlines of necrotic villi are seen in the mass, and with Weigert's fibrin stain it is found to be made up of stringy fibrin and of a lumpy, hyaline substance which does not stain like fibrin. With carbol-fuchsin and methylene blue tubercle bacilli in great numbers are found scattered throughout these larger masses. In a few places plume-like colonies of tubercle bacilli are found. Very few giant cells are found in the larger areas.

*Chorionic villi.*—The villi resemble those of a placenta of about the sixth or seventh month, the stroma showing but little myxomatous character, except in the younger offshoots, that of the larger villi resembling fibrous connective tissue. As mentioned above, tuberculous thrombi are in some cases attached to the syncytium, which shows no apparent changes, or in other cases to the denuded surface of the villus, which shows at such points an epithelioid proliferation with formation of giant cells and beginning caseation. Tubercle bacilli are found in scanty numbers in these, and also rarely free in the intercellular spaces of villi, showing no histological changes. In the chorionic vessels of both large and small size numerous thrombi resembling those of the intervillous spaces are seen. These also contain tubercle bacilli. No changes in the intima of such thrombosed vessels can be made out. In the majority of cases the thrombus is not attached to the vessel wall. On the whole, the villi show relatively slight change, the most striking findings being those of the intervillous spaces. The usual infarcts of the villi are present in perhaps an excessive degree.

*Decidua.*—The so-called decidual septa, as well as the upper portion of the decidua serotina, show areas of caseation — necrosis, collections of disintegrating leucocytes, and masses of fibrin. In these areas tubercle bacilli are also abundant.

In regard to the origin of the giant cells in the agglutination thrombi, it would seem that the majority are derived from leucocytes. Smaller multinuclear cells resembling transitional cells occur. No evidence could be found of their origin from syncytium. In the villi whose stroma was involved the appearances suggested an origin from the connective-tissue cells.

*Bacteriological.*—Staining of placental sections showed the presence of great numbers of tubercle bacilli, the majority in the maternal blood, but occurring also in the chorionic tissues and in the fetal circulation.

On October 22 a guinea pig was inoculated intraperitoneally with a thick beef-tea suspension of placenta. At the same time many smears of placental blood were stained for tubercle bacilli, but none were found. The animal became ill within a week, with high temperature and loss of weight, and died on the forty-third day. Unfortunately the body was destroyed by the janitor before an autopsy was made, but the course of the animal's illness leaves practically no doubt as to the nature of its disease.

*Pathological diagnosis.*—Agglutination thrombi of intervillous spaces due to tubercle bacilli; tuberculosis of chorionic villi; tuberculous thrombi in chorionic vessels.

#### SUMMARY.

The important features presented by this case are: Woman in fifth month of pregnancy, with chronic tuberculosis of kidney and general miliary tuberculosis; abortion; death; tuberculous thrombosis of placental sinuses and intervillous spaces; tuberculosis of placenta; tuberculous thrombi in fetal blood; presence of free tubercle-bacilli in fetal circulation without histological changes.

A comparison of this case with the other cases of placental tuberculosis reported shows that the changes found in these cases are apparently identical with those described above; viz., that the so-called placental tubercles are for the chief part intervillous thrombi containing giant cells and showing caseation. It would appear that the first steps in the development of placental tuberculosis consists in the formation by tubercle bacilli in the intervillous spaces of thrombi composed of fibrin and agglutinated red cells, and that the villi appear to be secondarily involved. The fact that the thrombi, even when resting upon the syncytium, do not appear to damage it, except in those cases where the villus is almost entirely or wholly surrounded by the thrombus, as well as the more striking fact that the syncytium may even grow out upon or partly around the thrombi, speaks for a marked resisting power on the part of the syncytial layer against the tuberculous process. That this resistance is at last ineffectual is also shown by the destruction of both syncytium and stroma, and by the occurrence of tuberculous proliferation of the cells of the chorionic stroma. It is, therefore, highly probable that the origin of placental tuberculosis is largely or chiefly dependent upon intervillous thrombosis.

The presence of so many tubercle bacilli in the maternal sinuses and intervillous spaces, when none could be found elsewhere in the maternal blood-vessels, is a point of great significance. If tubercle bacilli or other micro-organisms gain access to the maternal circulation, it would seem reasonable to believe that, from the conditions in the placental sinuses—large amount of blood and relatively slow current—they would tend to collect in these blood-spaces and here give rise to pathological disturbances. Such, indeed, seems to have been the case in this instance. Here undoubtedly great numbers of bacilli were free in the general circulation, and these collecting in the placental sinuses, and caught in the fibrin there, multiplied, caused thrombosis, and excited tuberculous proliferation in the chorionic stroma. If such great numbers may collect here in the case of general miliary tuberculosis, is it not also probable that in cases of local or chronic tuberculosis in the mother, in which only a

few bacilli escape into the circulation, these few are also likely to collect in the uterine and placental sinuses? Their further development would depend then wholly upon their ability to multiply under the conditions present there. The germicidal action of the blood may suffice to inhibit or destroy small numbers, and it is probable that only under certain conditions, or when present in the blood in large numbers, their growth is possible.

If multiplication does take place, and agglutination and coagulation of the blood result, it is very probable that both of these processes serve, within certain limits, to protect the placental tissues against tuberculous involvement. If the number of bacilli is very great and many agglutination thrombi are formed, the villi become secondarily involved, possibly in part as the result of circulatory and nutritional disturbances. The microscopical appearances presented by our case certainly convey the impression that the syncytium possesses a greater degree of resistance to tubercle bacilli than does the stroma of the villus. If the latter become infected, it is the result of a passage of bacilli through an intact syncytium or through a surface of the villus denuded of its syncytium. It is impossible to say positively from our studies of this case that the former had actually happened. Villi with apparently intact syncytial covering were found with free tubercle bacilli in the spaces of the stroma; and epithelioid proliferation and giant cells were found under similar conditions. Therefore, it does not seem safe to go so far as to affirm that an intact syncytium will not permit the passage of bacteria.

In any case, this point is not of such great moment if it is true that a denuded chorionic surface will permit the passage of bacteria. It is generally assumed by those who regard the placenta as a secure filter against micro-organisms that the syncytium of the normal placenta is everywhere intact. Such is not the case. From its earliest period the chorion shows progressive atrophy and growth. Anemic infarcts are constantly present, and through such damaged areas bacillary transmission may occur. In the later months of pregnancy the placenta is a senile organ, containing many infarcts and many chorionic villi with damaged syncytium.

There are, therefore, opportunities for the passage of bacteria through such senile villi. In these cases it is very probable that the fibrinous deposit which forms over such villi is a very important factor in preventing such transmission.

As to the fetus, it seems remarkable that so many bacilli could be present in its circulation without causing changes other than those of thrombosis. This may be explained by a more recent passage of the bacilli through the placenta, the time being too short for changes to have occurred; or by the assumption of a diminished virulence on the part of the bacilli; or by a relative or absolute immunity on the part of the fetal tissues. The second consideration may be thrown out, as the inoculation of the guinea pig with fetal blood resulted in an unusually rapid and virulent infection. Further observations and investigations will be necessary to settle the important question of immunity of the fetal tissues. Can it be proved that such an immunity exists, and that tubercle bacilli may live for some time in the fetal tissues without causing histological changes, the theory of latent congenital tuberculosis will receive a tremendous impulse.

It must not be forgotten that evidence favoring this has already been advanced, and that several cases have been reported in which such latency of tuberculosis seemed very probable (see the case above of Doléris and Bourges, 1896). Such a latency in the case of congenital typhoid seems probable in the case described by Blumer, in which a child, born five months after the mother had typhoid, died of typhoid infection nine days after birth. The apparent immunity of the fetal tissues to a number of poisons is also well known.

#### CONCLUSIONS.

1. In the case of the entrance of tubercle bacilli (miliary tuberculosis or chronic tuberculosis) or other micro-organisms into the maternal blood during pregnancy, the conditions of the circulation in the placental and uterine sinuses favor their collection there.

2. If the bacilli are capable of multiplication, the first step in the development of tuberculosis of the placenta appears to be an

agglutination and coagulation thrombosis of the maternal blood in the intervillous spaces. The formation of such thrombi around the multiplying bacilli may to some degree be protective in inhibiting or restricting their growth.

3. The syncytium appears to possess a certain degree of resistance against tubercle bacilli, the tuberculous thrombi in many cases being attached to an apparently normal syncytium, and occasionally the latter may even be found extending over the thrombus.

4. The question of the passage of tubercle bacilli through an apparently normal syncytium still remains open.

5. In the case of destruction of the syncytial covering, the stroma of the chorionic villi may become involved in a tuberculous process either directly or by an extension from a tuberculous thrombus. The syncytium of the normal placenta is not intact throughout, processes of decay and growth occurring in the chorionic villi from the earliest stages of pregnancy. In the later months the placenta is a *senile* organ, presenting in many places an atrophic or necrotic syncytium (infarcts), and through such damaged areas a passage of micro-organisms may take place. The deposit of fibrin found so frequently over such damaged areas may exert a protective action against such passage.

6. Tubercle bacilli may be found free in the reticular spaces and blood-vessels of the chorionic villi without the occurrence of histological changes of tuberculosis.

7. The fetal blood may contain great numbers of tubercle bacilli without other changes than small agglutination thrombi being present in the fetus. Inoculation shows these bacilli to retain their virulence. From this it may be assumed that the fetal tissues are relatively immune to the action of the tubercle bacillus.

8. Granting such an immunity, it is possible that living tubercle bacilli may be present in the fetus and newborn child without exciting histological changes; and, developing some time after birth, may then give rise to characteristic tuberculous lesions. A true latent congenital tuberculosis therefore is both possible and probable; but additional investigations are necessary

PLATE VI.

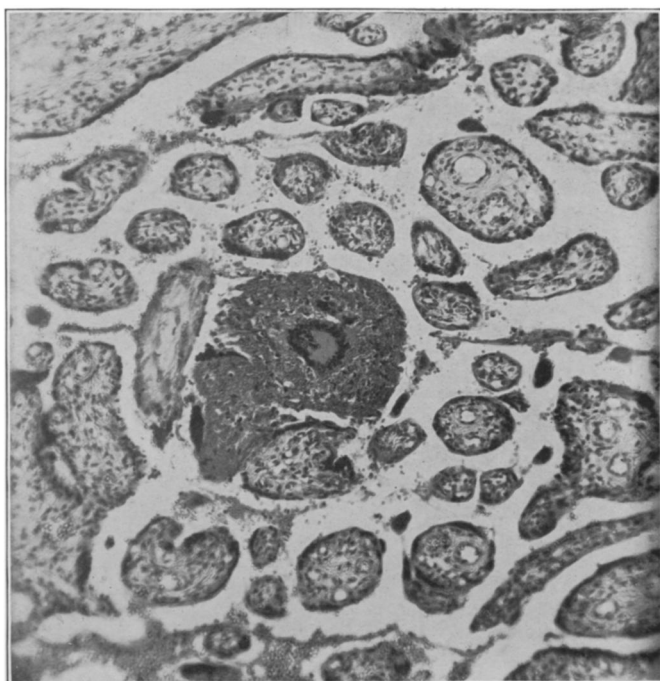


FIG. 1.

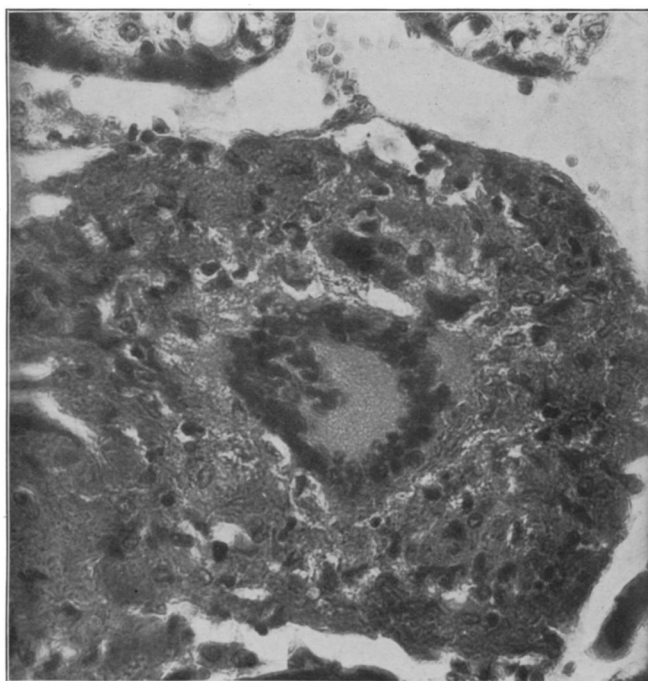


FIG. 2.

PLATE VII.

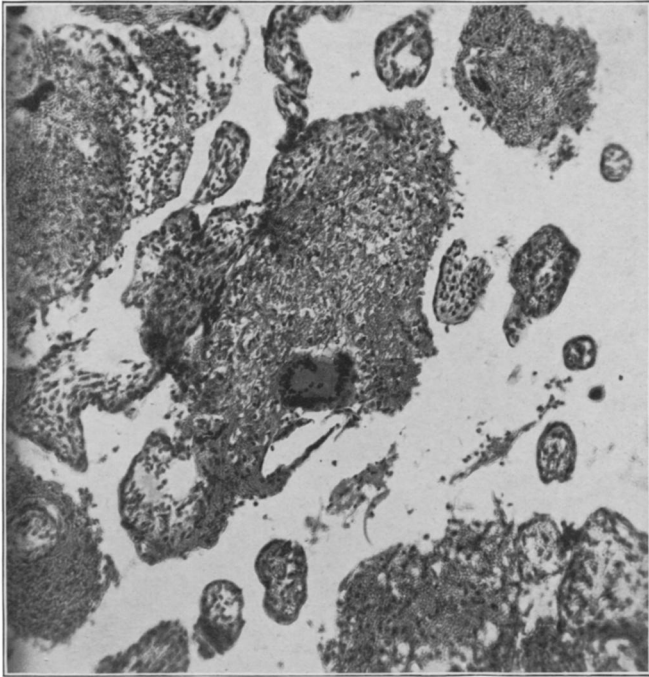


FIG. 3.

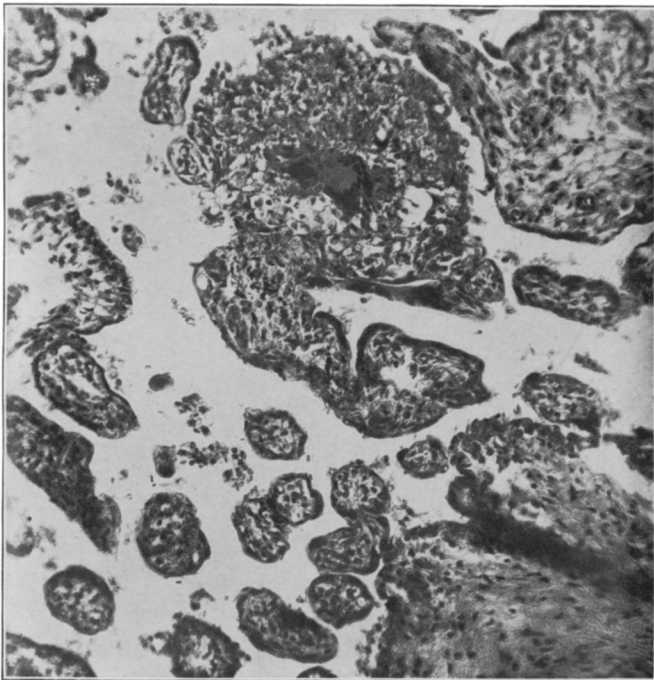


FIG. 4.



PLATE VIII.

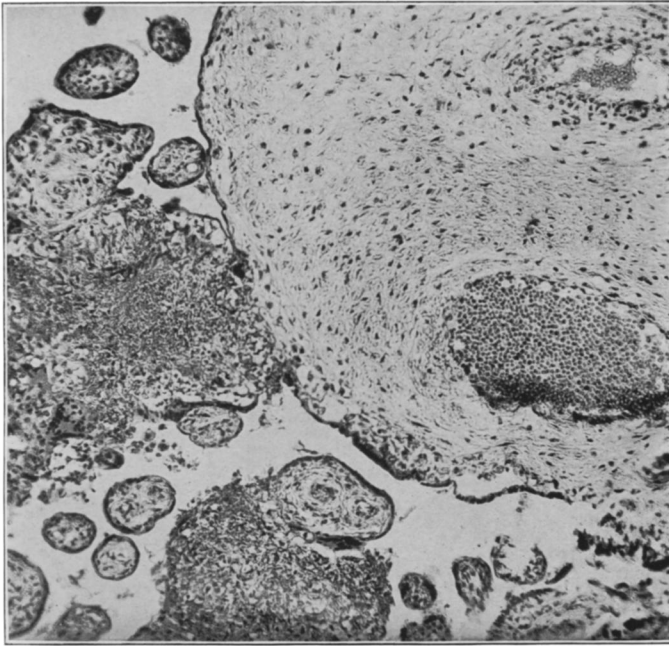


FIG. 5.

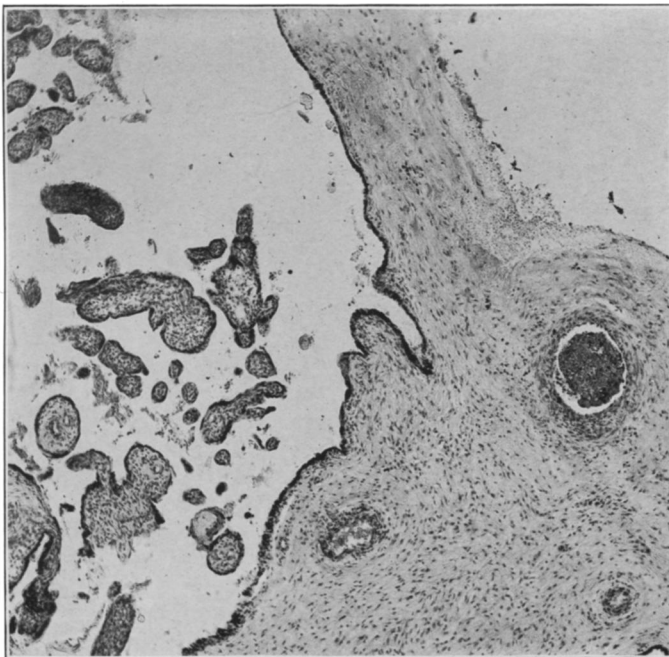


FIG. 6.

to settle the question of the frequency of such an event. The commonly accepted dicta regarding congenital tuberculosis are probably extreme. It is not at all unlikely that it is of much more common occurrence than is generally supposed.

#### EXPLANATION OF PLATES VI, VII, VIII.

FIG. 1.—Small agglutination thrombus in intervillous space. Thrombus is composed of red cells, fibrin and leucocytes. Large giant cell near center. Magnification: 135.

FIG. 2.—High-power view of tuberculous thrombus seen in Fig. 1. Magnification: 500.

FIG. 3.—Numerous agglutination thrombi in intervillous spaces. Outlines of red cells can be seen in several. Contained numerous tubercle bacilli. Magnification: 135.

FIG. 4.—Tubercle involving villus. Magnification: 175.

FIG. 5.—Tuberculous thrombus attached to chorionic stem. Syncytium absent at point of attachment, but can be seen extending over and around thrombus. Magnification: 135.

FIG. 6.—Chorionic stem with vessel (at right) containing agglutination thrombus. Numerous tubercle bacilli were found in thrombus. Magnification: 65.